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SCIENTIFIC ARTICLE

# Comparison of the effects of sugammadex and neostigmine on postoperative nausea and vomiting☆

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**KEYWORDS**
Sugammadex;
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**Abstract**
*Background and objectives:* The aim of our study is to compare the effects of sugammadex and neostigmine, used for neuromuscular blockage antagonism, on postoperative nausea and vomiting (PONV).
*Methods:* Our study was completed with 98 ASA I-II risk patients undergoing endotracheal intubation under general anesthesia. At the end of the surgery patients were randomly divided into two groups given 2 mg kg$^{-1}$ sugammadex (Group S) or 50 μg kg$^{-1}$ neostigmine plus 0.2 mg kg$^{-1}$ atropine (Group N). Monitoring and recording times were set as 1 hour postoperative and from 1–6, 6–12, and 12–24 hours. The anti-emetic amounts administered were recorded.
*Results:* In the first hour postoperative 13 patients in Group N (27%) and 4 in Group S (8%) were observed to have nausea and/or vomiting and the difference was statistically significant ($p = 0.0016$). During the 24 hours of monitoring there was no significant difference in the incidence and severity of PONV ($p > 0.05$), however the number of patients given ondansetron for PONV treatment in Group N was statistically significantly higher than the number in Group S (16 in Group N, 6 in Group S, $p < 0.011$).
*Conclusions:* At the end of our study comparing neostigmine with sugammadex for neuromuscular blockage antagonism, we found use of sugammadex had lower incidence of PONV in the postoperative 1st hour and less anti-emetic use in 24 hours of monitoring.


☆ This study was carried out at Ordu University Education and Training Hospital.

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**PALAVRAS-CHAVE**
Sugammadex;
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Pós-operatório;
Náusea;
Vômito

**Comparação dos efeitos de sugamadex e neostigmina em náusea e vômito no pós-operatório**

**Resumo**
*Justificativa e objetivos:* O objetivo de nosso estudo foi comparar os efeitos de sugamadex e neostigmina, usados para o antagonismo do bloqueio neuromuscular em náusea e vômito no pós-operatório (NVPO).
*Métodos:* O estudo foi concluído com 98 pacientes de risco ASA I-II, submetidos à intubação traqueal sob anestesia geral. Ao final da cirurgia, os pacientes foram aleatoriamente divididos em dois grupos que receberam 2 mg kg$^{-1}$ de sugamadex (Grupo A) ou 50 μg kg$^{-1}$ de neostigmina mais 0,2 mg kg$^{-1}$ de atropina (Grupo N). Os tempos de monitoração e registro foram definidos como 1 hora de pós-operatório e de 1-6, 6-12 e 12-24 horas. As quantidades administradas de antieméticos foram registradas.
*Resultados:* Na primeira hora de pós-operatório, 13 pacientes do Grupo N (27%) e 4 do Grupo S (8%) apresentaram náusea e/ou vômito e a diferença foi estatisticamente significativa ($p = 0,0016$). Não houve diferença significativa na incidência e gravidade de NVPO ($p > 0,05$) durante as 24 horas de monitoração, porém o número de pacientes que recebeu ondansetron para o tratamento de NVPO no Grupo N foi estatística e significativamente maior que o número de pacientes no Grupo S (16 e 6, respectivamente, $p < 0,011$).
*Conclusões:* Ao final do estudo quando comparamos neostigmina com sugamadex para o antagonismo do bloqueio neuromuscular descobrimos que sugamadex apresentou menor incidência de NVPO na primeira hora de pós-operatório e consumo menor de antiemético em 24 horas de monitoração.


## Introduction

Postoperative nausea and vomiting (PONV) has been one of the most important problems of anesthesia through the years. Kapur[1] described PONV as the ''Big Little Problem'' in 1991. While Watcha[2] touched on Kapur's definition, he summarized his own views of PONV as the ''Big Big Problem''. PONV is one of most common complications after general anesthesia that may cause increased morbidity and prolonged hospital stay.[3] Duration of anesthesia, type of surgery, postoperative analgesia with opioids, as well as patient related factors such as age, gender, smoking habits and previous history of PONV and of motion sickness are known as risk factors for developing PONV.[3–5]

Neuromuscular blocker medications are a necessary part of general anesthesia. Additionally at the end of the surgical procedure the majority of times the residual neuromuscular block is reversed with acetyl choline esterase inhibitors.[6] Cholinesterase inhibitors have been implicated in the development of PONV as a result of their potent muscarinic effects upon the gastrointestinal tract and the vomiting center in the brain.[7] Neostigmine, used at the end of surgery for residual neuromuscular block, is associated with increased the risk of PONV, especially when used in large doses (>2.5 mg).[7] Some previous studies have recommended avoiding the use of acetyl choline esterase inhibitors to reduce postoperative vomiting.[8]

Sugammadex is a γ cyclodextrin agent that selectively binds steroidal neuromuscular blockers such as rocuronium. By making complexes with rocuronium in circulation and at neuromuscular junction, it enables the excretion of the drug in the urine without metabolization.[9] Sugammadex gives rise to safe and rapid reversal of neuromuscular blockade induced by rocuronium.[10,11] Sugammadex is known as a safe drug without any known serious side effects. The common side effects of sugammadex are minimal cough, oral discomfort, hypersensitivity, temporary QT prolongation and temporary (<30 min) activated partial thromboplastin time prolongation.[12] The studies on the effects of sugammadex on PONV are very limited.[13]

The hypothesis of our study is that use of sugammadex to antagonize the effects of neuromuscular blocker agents will reduce postoperative nausea and vomiting when compared with neostigmine. With the aim of testing this hypothesis we aimed to compare the effects of 2 mg kg$^{-1}$ sugammadex and 50 μg kg$^{-1}$ neostigmine on the incidence of PONV. We defined the major outcome as presence of PONV at the postoperative one hour period and number of patients who were needed ondansetron for symptomatic treatment during 24 hours postoperative period.

## Method

This single-blind prospective randomized controlled study was conducted at ninety-six ASA I and II patients, aged in between 18 and 65 years, scheduled to have general anesthesia with endotracheal intubation for elective surgery. The study was approved by Ethics Committee of University School of Medicine (2014/515) and Clinical Trials study report (NCT) and conducted in accordance with the

Declaration of Helsinki. Written informed consent was obtained from all patients participating in the study.

Exclusion criteria were including neurosurgery, laparoscopic, oncologic, gynecologic, breast, strabismus and mid ear surgery, history of drug and alcohol abuse, body mass index (BMI) > 30 kg $m^{-2}$, use of analgesics, sedative or antiemetic drugs within 24 hours before surgery, psychiatric and neurological disorders, allergy or contraindication of study drugs. Additionally patients with more than two hours surgery time were also excluded.

No preanaesthetic medication was administered. In the operating room, patients were monitored with ECG, non-invasive arterial pressure, peripheral $O_2$ saturation ($SpO_2$) and end-tidal $CO_2$ levels (Mindray, BeneView T8, Shenzhen, PR China). An intravenous line of 10 mL $kg^{-1}$ ringers lactate solution was infused via 20G venous cannula through the dorsum of the non dominant hand. Using a computer generated sequence of numbers and a sealed envelope technique, patients were randomly divided into 2 groups: patients who received neostigmine/atropine combination (Group N, $n = 50$) or sugammadex (Group S, $n = 50$) for reversal of neuromuscular blockade. Neuromuscular monitoring was carried out using TOF Watch SX® (Organon Ltd., Dublin, Ireland) acceleromyography, with skin electrodes located at the ulnar nerve trace for contractions of adductor pollicis muscle.

Before the operations to assess the PONV risks of patients, the simplified Apfel scoring system was used: (gender: male:0, female:1) + (history of PONV or motion sickness: no:0, yes:1) + (smoking status: no:0, yes:1) + (anticipated use of postoperative opioids: no:0, yes:1).[14] Patients with a score of two were given 4 mg iv dexamethasone (Deksamet 8 mg/2 mL, Osel İlaç, Beykoz, İstanbul) before induction, while patients with a score of 3 and above were additionally given 4 mg iv ondansetron (Ondaren 4 mg/2 mL, Vem İlaç, Mecidiyeköy, İstanbul) at the end of surgery.[15]

General anesthesia was induced by iv 1 μg $kg^{-1}$ fentanyl and 2.5 mg $kg^{-1}$ propofol. With the loss of consciousness (loss of eyelash reflex), iv 0.6 mg $kg^{-1}$ rocuronium was applied. Orotracheal intubation was performed when no response was yielded with Train of Four (TOF) stimulation of TOF-Guard. After intubation the patient was mechanically ventilated in the controlled mode where the end-tidal $CO_2$ pressure was kept between 35 and 40 mmHg. Anesthesia was maintained with 2% sevoflurane in 50% $O_2$/air mixture and 0.2–0.7 μg $kg^{-1}$ $min^{-1}$ iv remifentanil infusion. Additional iv bolus of 0.1–0.2 mg $kg^{-1}$ rocuronium was administered during surgical procedure provided that TOF ratio to be 10% or lower. No neuromuscular blocker agent was used if the remaining time to the end of surgery was less than 30 minutes. At the end of the surgery, anesthetic drug administration was ceased and the patient was manually ventilated with 100% oxygen. According to the randomization schedule, antagonization of neuromuscular blockade was provided with intravenous administration of 0.05 mg $kg^{-1}$ neostigmine and 0.02 mg $kg^{-1}$ atropine for the patients in Group N and 2 mg $kg^{-1}$ sugammadex for the patients in Group S when reappearance of the second twitch (T2) on the TOF. The patients were extubated after aspiration of oropharyngeal secretions with the 90% recovery of TOF value. Additional iv administration of 0.025 mg $kg^{-1}$ neostigmine and 0.01 mg $kg^{-1}$ atropine in Group N and 2 mg $kg^{-1}$ sugammadex in Group S was planned in case of need (should the TOF value stay under 90% after 5 minutes).

In all patients iv 1 gr paracetamol (Parol 10 mg $mL^{-1}$, Atabay, Kadıköy, İstanbul) infusion was administered for postoperative analgesia at end of the surgery and every 8 hours in first postoperative day. Pain was assessed using a visual analog scale (VAS) from 1 to 10. Intravenous 50 mg dexketoprofen (Arveles 50 mg/2 mL, Ufsa İlaç, Topkapı, İstanbul) was given on when VAS score >4. Administration of iv 1 mg $kg^{-1}$ tramadol (Contramal 50 mg $mL^{-1}$, Aİ, Sarıyer, İstanbul) for postoperative analgesia were planned as rescue agents.

The patients were monitored and assessed for 24 hours; hourly for the first 6 hours, every 2 hours in the 6–12 hours interval and, subsequently, every 4 hours. They were asked specifically about pain, nausea, vomiting and other side effect. In all patients, nausea and vomiting were assessed by the same researcher (NT) using a four point verbal descriptive scale as described in previous studies: 0 = not nauseated, 1 = nauseated, not vomiting, 2 = nauseated, one to two episodes of vomiting, 3 = nauseated, more than two episodes of vomiting during the observation period).[16]

In the presence of continuing nausea (>5 min) or active vomiting, iv 4 mg ondansetron was administered, if not given as prophylactic. If ondansetron was previously administered the medication was not given again within 6 hours but metoclopramide 0.2 mg $kg^{-1}$ was given instead.

Patient characteristics, type of surgery, amount of opioid consumption and duration of anesthesia were recorded. Complications after the surgery such as headache, cough, respiratory depression, hypertension, bradycardia, sore throat, gastrointestinal system complaints were also noted. HR below 50 pulse $min^{-1}$ was considered as bradycardia and managed with 0.5 mg iv atropine. MAP above 125 mmHg was considered as hypertension and managed with 0.1 mg iv nitroglycerin.

## Power analysis

In a previous study,[16] the incidence of PONV was reported as 30% with the same neostigmine dose as our study while it was 11% with placebo. According to an evaluation based on a this study, 44 patients in each group would be required in order to detect 20% change with 80% power and 5% significance ($\alpha = 0.05$, $\beta = 0.80$) in two way significant interactions (Minitab 13.1 Inc., State College, PA, USA). We planned to include 100 patients in this study to allow for dropouts.

## Statistical analysis

Data obtained in the study were analyzed with SPSS 16.0 (IBM SPSS Statistics, Chicago, IL, USA). Descriptive statistics were stated as mean ± standard deviation for continuous variables and as number and percentage for nominal variables. Distribution analysis was made with the Kolmogorov–Smirnov test. Age, BMI, remifentanil consumption, surgery time were evaluated with student *t* test. The Chi-square or the Fisher exact test was used for categorical data such as gender, ASA physical status, rate of PONV,

**Table 1** Patients and clinical characteristics.

| | Group N $n=48$ | Group S $n=50$ | $p$ |
|---|---|---|---|
| Age (yr) | 40.8 ± 11.2 | 40.3 ± 13.3 | NS |
| Weight (kg) | 73 ± 9.2 | 71 ± 10.5 | NS |
| BMI (kg m$^{-2}$) | 23.9 ± 3.5 | 22.8 ± 3.6 | NS |
| Gender (F/M) | 18/30 | 16/34 | NS |
| ASA I/II | 37/11 | 36/14 | NS |
| Apfel score 0/1/2/3 (*n*) | 14/20/14/0 | 16/19/15/0 | NS |
| Surgery time (min) | 49.9 ± 22.3 | 54.7 ± 22.0 | NS |
| Remifentanil consumption (μg) | 624 ± 196 | 681 ± 186 | NS |

NS, not significant; BMI, Body mass index; F/M, female/male; ASA, American Society of Anesthesiologist.
Data are presented as mean ± SD or frequencies.

side effects. A value of $p < 0.05$ was accepted as statistically significant.

## Results

The study included two groups with 50 patients in each group. Two patients in Group N were excluded from the study as their surgeries lasted more than 2 hours. The demographic data in both groups were similar (Table 1). There was no significant difference between the patients in terms of PONV risk scores, surgical durations and consumed remifentanil amounts (Table 1). In Group N, 24 patients (50%) underwent head and neck surgery, 13 (27%) had urology, 4 (8%) had orthopedic and 7 patients (15%) had general surgery procedures. In Group S, 29 patients (58%) had head and neck surgery, 11 (22%) had urology, 5 (10%) had orthopedic and 5 patients (10%) had general surgery procedures. There was no statistically significant difference between the groups in terms of type of surgery undergone ($p > 0.05$).

In the post anesthesia care unit (PACU) during 1 hour postoperative monitoring, 13 patients in Group N (27%) and 4 patients in Group S (8%) had nausea and/or vomiting. The rate was higher by a statistically significant degree in Group N ($p = 0.016$). In the later 24 hour monitoring, there was no statistically significant difference observed in the incidence and severity of PONV between the groups ($p > 0.05$, Table 2). However the number of patients given ondansetron in Group N was significantly high (16 patients in Group N, 6 in Group S, $p = 0.011$). The postoperative analgesic treatments in both groups were similar (Table 2). There was no significant difference between the groups in terms of side effects (Table 3).

**Table 2** Incidence and severity of PONV and antiemetic and analgesic treatment in groups.

| | Group N $n=48$ | Group S $n=50$ | $p$ |
|---|---|---|---|
| *PONV at PACU* | | | 0.016 |
| No | 35 (73%) | 46 (92%) | |
| Yes | 13 (27%) | 4 (8%) | |
| *PONV at PACU* | | | NS |
| 0 | 35 (73%) | 46 (92%) | |
| 1 | 9 (19%) | 3 (6%) | |
| 2 | 3 (6%) | 1 (2%) | |
| 3 | 1 (2%) | 0 | |
| *1–6 hours* | | | NS |
| 0 | 43 (90%) | 48 (96%) | |
| 1 | 4 (8%) | 2 (4%) | |
| 2 | 1 (2%) | 0 | |
| *6–12 hours* | | | NS |
| 0 | 45 (94%) | 50 (100%) | |
| 1 | 3 (6%) | 0 | |
| 2 | 0 | 0 | |
| *Antiemetic treatment (n) (Ondansetron)* | 16 (33%) | 6 (12%) | 0.011 |
| *Analgesic treatment (n) (Dexketoprofen)* | 14 (30%) | 17 (34%) | NS |
| *Analgesic treatment (n) (Tramadol)* | 3 (6%) | 4 (8%) | NS |

Data are presented as frequencies. PONV, Postoperative nausea and vomiting; PACU, Postanesthetic care unit. PONV was evaluated as follows: 0 = not nauseated, 1 = nauseated, not vomiting, 2 = nauseated, one to two episodes of vomiting, 3 = nauseated, more than two episodes of vomiting.

**Table 3** Postoperative side effects.

| | Group N $n=48$ | Group S $n=50$ | $p$ |
|---|---|---|---|
| Headache | 4 (8%) | 2 (4%) | NS |
| Hypertension | 2 (4%) | 3 (6%) | NS |
| Bradycardia | 2 (4%) | 0 | NS |
| Coughing | 2 (4%) | 0 | NS |
| Shivering | 0 | 1 (2%) | NS |
| Sore throat | 1 (2%) | 0 | NS |
| Respiratory depression | 2 (4%) | 0 | NS |

Data are presented as frequencies.

## Discussion

In our study comparing the effects of sugammadex and neostigmine, used to antagonize the effects of neuromuscular blocker agents, on incidence of postoperative nausea and vomiting, less PONV was observed in the first hour postoperative with the use of sugammadex compared to neostigmine. Our cases administered sugammadex had a significant reduction in the amount of anti-emetics used in the first 24 hours postoperative compared with cases administered neostigmine.

Many studies have reported the emetic effect of the use of high-dose neostigmine for neuromuscular blockage antagonism. King et al.[17] in a study researching the effects of neostigmine on PONV, administered one group neostigmine-atropine for neuromuscular blockage antagonism and used no medication for the other group. In conclusion they identified a significant difference with higher nausea by 68% to

32% and vomiting by 47% to 11% in the neostigmine-atropine group. Ding et al.[18] studied laparoscopic tubal ligation and found significantly more PONV in the PACU when neostigmine was compared with placebo after mivacurium, 65% versus 25% respectively. Meta-analyses demonstrate that high-dose neostigmine (>2.5 mg) is associated with increased PONV and that reducing the dose can decrease PONV risk.[7,19]

However, the clinical importance of neostigmine's effects on PONV has been questioned. The results of a meta-analysis study including 15 studies, found the evidence that neostigmine increased the risk of PONV to be insufficient.[20] A study researching the effects of neostigmine on PONV after abdominal hysterectomy operations left one group to spontaneously recover from neuromuscular blockage induced by mivacurium while the other group was antagonized with 2 mg neostigmine. They did not find a significant difference between the groups in terms of both nausea and vomiting. In conclusion they stated that the use of neostigmine for neuromuscular block antagonism did not increase the incidence or severity of PONV.[21] It has been reported that neuromuscular block antagonism with 2 mg neostigmine in laparoscopic gynecological operations did not cause an increase in the incidence of PONV.[22] The noticeable point in these two studies is the amount of neostigmine used. It has been determined that use of neostigmine in doses above 2.5 mg increases the risk of PONV.[7,15-17]

A study by Lovstad et al.[16] compared the effect of 50 $\mu g\,kg^{-1}$ dose of neostigmine with a placebo group on PONV in women after laparoscopic gynecology operations. At the end of surgery all patients were given iv 0.05 $mg\,kg^{-1}$ ondansetron. In the first 6 hours they found the nausea rate in the neostigmine group was 30%, while in the placebo group this rate was 11%. The necessity for rescue anti-emetic medication (metoclopramide 0.2 $mg\,kg^{-1}$ and droperidol 0.025 $mg\,kg^{-1}$) was 28% in the neostigmine group and 7% in the placebo group. They reported that both these differences were statistically significant. The researchers did not find a significant difference in vomiting rates in the first 6 hours. Monitoring from 6 to 24 hours, the so-called late period, observed no significant difference in either nausea or vomiting. In conclusion this study reported that high dose neostigmine for neuromuscular blockage antagonism caused an increase in the risk of nausea in the first 6 hours after surgery for women undergoing laparoscopic surgery, even with ondansetron prophylaxis. The dose of neostigmine used in this study, when the weight of the patients in the study is taken into account, is above the 2.5 mg dose stated to cause an increased risk of PONV.

The studies assessing the effect on postoperative nausea and vomiting when sugammadex and neostigmine are used to reverse the effect of neuromuscular blocker agents are very limited. According to the results of a study assessing postoperative results of neuromuscular blockage antagonism and including 1440 patients (772 sugammadex, 212 neostigmine, 510 no reversal), the incidence of PONV in the PACU was found to be significantly high in the neostigmine group compared to the sugammadex group (21.5% vs. 13.6%, $p < 0.05$). The researchers did not determine any significant difference between the sugammadex and no-reversal groups. In a study which reported the use of intraoperative anti-emetics was more frequent in the neostigmine group, they emphasized that the cause of increased risk of PONV in the sugammadex group was urgent surgery and abdominal surgical procedures. When the researchers assessed the results of the study they stated that the cost increase caused by use of sugammadex was off-set by the reduction in incidence of PONV.[23]

A study by Koyuncu et al.[13] compared the effects of 70 $\mu g\,kg^{-1}$ neostigmine and 2 $mg\,kg^{-1}$ sugammadex on PONV when used for neuromuscular blockage antagonism in 100 patients undergoing extremity surgery. In the study with induction of anesthesia using propofol, fentanyl and rocuronium while maintenance used desflurane and nitrous oxide with oxygen, 0.5 $mg\,kg^{-1}$ iv meperidine was administered at the end of surgery for postoperative analgesia. They did not administer intraoperative anti-emetic medication. PONV was treated with 4 mg ondansetron iv and if it continued 10 mg metoclopramide iv. When the findings of the study are evaluated, though there was no difference in anesthesia durations and Apfel scores of patients, they stated that the nausea and vomiting scores in the PACU were statistically significantly lower in the sugammadex group. However during 24 hours postoperative nausea and vomiting was observed in 60% of the sugammadex group and 58% of the neostigmine group and they reported there was no significant difference. In conclusion comparing sugammadex with neostigmine they determined that there was a slight and temporary reduction in the incidence of PONV. They did not find a positive effect of the return of gastrointestinal functions and ambulation. The researchers linked their high rates of PONV, when compared to the literature, to the use of nitrous oxide for anesthesia maintenance and the use of opioids for postoperative analgesia.[13]

The results of our study are similar to the study by Koyuncu et al.[13] in identifying a lower PONV incidence in the 1st hour of monitoring in PACU with sugammadex. However in the 24 hour monitoring period, the study by Koyuncu et al. had different and higher results than in the literature and our study. In our study during the postoperative 1–6 hours the nausea and vomiting incidence was 10% in Group N and 4% in Group S, while between 6 and 24 hours it was found to be 6% in Group N and 0% in Group S. We believe the basic reason for the differences from the results of Koyuncu et al. is that in situations with Apfel score of 2 and above we administered antiemetic medication. Another important reason may be the amount of neostigmine used. Koyuncu et al. used 70 $\mu g\,kg^{-1}$ in their study. In our study the dose of neostigmine was 50 $\mu g\,kg^{-1}$, which is similar to many studies in the literature.[7,16,20] When the mean weights are considered, the mean amount of neostigmine used per patient in our study was 3.65 mg, while this was 5.25 mg in the study by Koyuncu et al. Other possible reasons may be listed as differences in anesthetic method (we did not use $N_2O$ for maintenance or meperidine for postoperative analgesia) and our shorter duration of surgery (about 30 minutes shorter). It has been determined that the increase in surgical duration may increase the incidence of PONV (each 30 min increase in duration increases PONV risk by 60%, so that a baseline risk of 10% is increased by 16% after 30 min).[10]

In our study in the postoperative 24 hour monitoring period, the number of patients given anti-emetic treatment with ondansetron was significantly lower in the sugammadex group (12% compared to 33%). Ledowski et al.[23] in a retrospective scan reported similar results, with lower

anti-emetic medication administration in the PACU for the sugammadex group.

The most important limitation of our study is that though we did not include surgeries known to be risk factors for PONV, it was not completed with a single type of surgery.

In conclusion, this study shows that neostigmine reversal in increased PONV at PACU and use of antiemetic rescue medication during the postoperative 24 hours. In terms of PONV, the use of sugammadex for neuromuscular blockage antagonism may be a better choice for patients with high risk or where this situation is undesirable.

## Clinical trial registration

NCT02286752.

## Ethics committee approval

Ethics committee approval was received for this study from Ethics Committee of Ondokuz Mayıs University (2014/779).

## Conflicts of interest

The authors declare no conflicts of interest.

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